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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,847	02/25/2004	David C. Gan	03.47	2937

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EXAMINER	
VENKAT, JYOTHSNA A	

ART UNIT	PAPER NUMBER
1619	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,847	GAN ET AL.	
	Examiner	Art Unit	
	JYOTHSNA A. VENKAT	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13,17-19,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25-26* is/are allowed.

6)☒ Claim(s) *1-4,13 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/9/08 has been entered.

Receipt is acknowledged of amendment and remarks filed on 10/9/08. Claims 25-26 have been added as per applicants' amendment dated 10/9/08. Claims 20-24 are withdrawn from consideration as being drawn to non-elected invention. Claims 1-4, 13 , 17-19 and 25-26 are currently examined in the application.

Claim Rejections - 35 USC § 112

Claims 1- 4, 13 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". See ***In re Wands, 858 F.2d 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1998).*** The court set forth the eight factors to consider when assessing if a disclosure would require undue experimentation. Citing *Ex parte Forman, 230 USPQ 546*, the court recited eight factors

These factors include, but are not limited to:

1) *The breadth of the claims,*

2) *The nature of the invention,*

3) *The state of the prior art,*

4) *The level of one of ordinary skill,*

5) *The level of predictability in the art,*

6) *The amount of direction provided by the inventor,*

7) *The existence of working examples*

8) *The quantity of experimentation needed to male or use the invention based on the content of the disclosure.*

(1 and 2) The breadth of the claims and the nature of the invention: *The claims are drawn to:*

1. A method for increasing DNA synthesis of dermal papilla cells in hair follicles which comprises applying to the cells a composition containing a follicle-stimulating effective amount of a creatine compound or

13. A method for stimulating hair growth in hair plugs, which comprises applying to the hair plugs, a follicle-stimulating effective amount of a creatine compound.

(3 and 5) The state of the prior art and the level of predictability in the art: *The art is unpredictable with respect to stimulating hair growth.*

(6-7) The amount of direction provided by the inventors and the existence of working examples

Specification under paragraph 21admits that certain concentration is effective in growing dermal papilla cells. See below.

[0021] **Results:** Creatine was found to significantly increase DNA synthesis in papilla cells (see Tables 1&2). At 0.25mM, creatine induced a 36% increase in DNA synthesis. At 0.5mM, creatine induced a 25% increase in DNA synthesis. At 1mM, creatine induced a 6% increase in DNA synthesis. Oxaloucetate was also found to significantly increase DNA synthesis in papilla cells in a dose dependent manner. At 0.25mM, Oxaloacetate induced a 22% increase in DNA synthesis. At 0.5mM, Oxaloacetate induced a 33% increase in DNA synthesis. At 1mM, Oxaloacetate induced a 38% increase in DNA synthesis. Positive results have also been observed with equivalent concentrations of AMP(1493% increase at .25 mM, 1930% at 0.5 mM, 1449% at 1 mM) and ATP(1411% increase at .25 mM, 1201% at .5 mM).

See below with respect to example 2.

[0023] **Example 2**. This example illustrates the increase in hair growth observed in hair plugs exposed to creatine.

[0024] **Methods:** Hair plugs were obtained from East Wood Medical Hair Transplant Surgery (Garden City, NY). These hair plugs were equilibrated in hair plug media as described in the literature (DMEM, 10% FBS, 1% PS, 25mg insulin, 25 µg fungizone). These hair plugs were measured under the microscope one the first day of arrival and treated with creatine at 1mM (n=6 for control and creatine group respectively). These hair plugs were then kept in the incubator at 37°C in 5% CO_2. On day 3, 7, & 10, re-treatments were made as well as measurements.

[0025] **Results:** The hair plugs were found to grow at a constant rate. In the untreated group, there was an average growth of 0.48mm at day 3 compared to day 0. There was an average growth of 0.73mm at day 7, and an average growth of 0.82mm at day 10. Creatine was found to significantly increase the growth rate of these hair plugs compared to the untreated plugs. There was an average growth of 0.95mm at day 3, 1.32mm at day 7, and 1.43mm at day 10 (Refer to Table 3, 4, and 5). These increases were all statistically significant.

[0026] **Discussion:** Creatine was found to significantly increase hair growth in hair plugs. This increase was nearly two fold compared to the untreated plugs. We previously observed creatine increasing DNA synthesis in dermal papilla cells. As dermal papilla cells influence and modulate the growth of hair, we postulate that creatine may be increasing hair plug growth by increasing the activity of dermal papilla cells.

Thus specification teaches that dermal papilla cell influence the hair growth. Test results showed that creatine induced 36% increase in DNA synthesis at 0.25 mM concentration. When the concentration was doubled there is 25% increase in DNA synthesis, and when the concentration was at 1 mM creatine induced 6% increase in synthesis. Therefore as the concentration of creatine increases the DNA synthesis value decreases. Claim 1 doe snot recite any concentration. This value can be any molar concentration. The concentration can be any value greater than 1. If the concentration is 2 mM there might not be increase in DNA synthesis. Test showed only values for creatine. Creatine compound can be any derivative creatine. There is no structural similarity between creatine and cyclocreatine. The compound

tested with respect to hair growth was in vitro and the results are with respect to creatine and not its metabolite creatine phosphate or cyclocreatine.

Regarding stimulating hair growth in hair plugs, test results at paragraph 24 used creatine at 1 mM concentration. At this concentration DNA synthesis was only 6%. *What is the reason for using this concentration, when the DNA synthesis is less compared to 0.25 mM concentration*? There is no correlation between the test results for DNA synthesis and stimulating hair growth in hair plugs. Stimulating hair growth was done using creatine and not any creatine compound.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: the art is unpredictable with respect to hair growth. There is no correlation between the test results for DNA synthesis and stimulating hair growth in hair plugs. The instant specification gives one skilled in the art no indication that the one could use any amount of creatine or any amount of creatine phosphate or any amount of cyclocreatine and increase DNA synthesis and stimulate hair growth in hair plugs and have a reasonable expectation of success. The instant specification gives one skilled in the art no indication that the one could use any amount of creatine or any amount of creatine phosphate or any amount of cyclocreatine and stimulate the hair growth or increase DNA synthesis. Therefore further testing would be necessary to use the claimed invention and the practice of the full scope of the invention would require undue experimentation.

Response to Arguments

Applicant's arguments filed 10/9/08 have been fully considered but they are not persuasive.

Applicants' argue:

"(2) The Creatine Compound to be Used

In the outstanding Office Action, the Examiner asserted that the creatine compound as recited by the pending claims of the present application "can be any derivative [off creatine," that "[t]here is no structural similarity between creatine and cyclocreatine," and that "the [testing] results are with respect to creatine and not its metabolite creatinephosphate or cyclocreatine" (see the Office Action, page 5, lines 8-1 1). However, it is never Applicants' intent that the claimed invention of the present application should cover any type of creatine derivatives or analogues, as Examiner asserted. On the contrary, the instant specification specifically defines the term "creatine compound(s)" as "creatine and creatine analogues that exhibit the same type of stimulatory activity" (see the instant specification, page 3, lines 19-20), which clearly and unequivocally imposes a limitation on the type of creatine derivatives or analogues that can be used in the claimed invention, i.e., such creatine derivatives or analogues have to exhibit follicle-stimulating activity.

It is well known that creatine phosphate can be readily converted in vivo to and from creatine by an enzyme called creatine kinase, which is present in all vertebrates (see attached information for "Creatine" downloaded from http://en.wikipedia.orglwiki/Creatine on October 8). Therefore, creatine phosphate, when applied to human skin or skin cells, can be

readily converted in vivo to creatine to stimulate the hair growth in follicles. Therefore, it is certain that creatine phosphate will exhibit the same type of stimulatory activity as creatine. Although cyclocreatine is structurally different from creatine, it has been well accepted as a functional analogue of creatine. Specifically, both creatine and cyclocreatine are substrates for mitochondrial creatine kinase, and cyclocreatine has been recognized as the most kinetically active analog of creatine in the creatine kinase reaction (see Matthews et al., "Neuroprotective Effects of Creatine and Cyclocreatine in Animal Models of Huntington's Disease," THE JOURNAL OF NEUROSCIENCE, January 1, 1998, 18(1):156-163). Therefore, it is highly likely that cyclocreatine will exhibit the same type of stimulatory activity as creatine. Further, it has been well established that the mere presence of certain inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled, as long as one skilled in the art could readily determine which embodiments would be inoperative or operative with reasonable experimentation. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 224 USPQ 409,414 (Fed. Cir. 1984). In the present case, even if assuming arguendo that cyclocreatine or some other known functional analogue of creatine was not effective in stimulating the hair growth in follicles, the enablement requirements under 35 U.S.C. §112, first paragraph can still be met, because one ordinarily skilled in the art can

readily follow the essay described in step-by-step detail by Example 2 of the instant specification to determine whether cyclocreatine or the other functional analogue of creatine constitutes the "creatine compound" within the meaning of claims 1-4, 13 and 17-19 of the present application, i.e., whether cyclocreatine or the other functional analogue of creatine is effective in stimulating hair growth in follicles or not. As mentioned hereinabove, such repetition of a well-described essay does not involve any inventive skill or constitute "undue" experimentation. Instead, it is merely routine experimentation for which the instant specification has already provided detailed, step-by-step instruction".

In response to the above argument, specification does not describe creatine analogues that exhibit the same type of stimulatory activity other than creatine phosphate and cyclocreatine. Examine reviewed the NPL document with respect to "Neuroprotective Effects of Creatine and Cyclocreatine in Animal Models of Huntington's Disease". Test results showed that as the concentration of creatine increased the DNA synthesis value decreased. Therefore there is unpredictability with respect to DNA synthesis in dermal papilla cells. Admitted by applicants' at page 9 of the response only high concentration of creatine was effective in stimulating hair growth in hair follicles and not any other concentration , where as low concentration of creatine has stronger stimulatory effect for DNA synthesis. There is unpredictability regarding creatine with respect to DNA synthesis in dermal papilla cells and stimulating hair growth. Same concentration is not effective for both types of methods.

There is no description in the specification for creatine analogues other than creatine phosphate and cyclocreatine. Specification did not show any test results for any creatine compound other than creatine with respect to DNA synthesis in dermal papilla cells and stimulating hair growth. Therefore it is an undue experimentation to determine the suitable concentration for DNA synthesis in dermal papilla cells for all creatine compounds that is effective and also determine the suitable concentration for stimulating hair growth for all creatine compounds.

Claims 25-26 are allowed. Applicants' are also notified that if claims 25-26 are amended to recite in Markush group, creatine and creatine phosphate, claims will also be allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JYOTHSNA A. VENKAT whose telephone number is 571-272-0607. The examiner can normally be reached on Monday-Friday, 10:30-7:30:1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL WOODWARD can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JYOTHSNA A VENKAT /
Primary Examiner, Art Unit 1619